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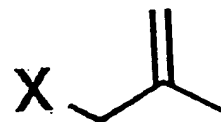
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(72) Inventors:

- **TENDO, Atsushi**
Kasukabe-shi, Saitama 344-0005 (JP)
- **TAKAHASHI, Toshihiro**
Misato-shi, Saitama 341-0003 (JP)
- **YAMAKAWA, Tomio**
Kashiwa-shi, Chiba 277-0884 (JP)

(30) Priority: **11.09.2002 JP 2002265335**(71) Applicant: **NIPPON CHEMIPHAR CO., LTD.****Tokyo 101-8678 (JP)**(74) Representative: **Albrecht, Thomas, Dr.****Kraus & Weisert,
Thomas-Wimmer-Ring 15
80539 München (DE)**(54) **AMINE DERIVATIVE**

(57) The invention relates to (1S)-1-isobutoxymethyl-3-methylbutylamine useful as an intermediate in the synthesis of sodium (2S,3S)-3-[[[(1S)-1-isobutoxymethyl-3-methylbutyl]carbamoyl]oxirane-2-carboxylate and a process for production thereof. The process comprises reacting L-leucinol with a compound represented by the following formula in the presence of a base and reducing the obtained (1S)-1-(2-methyl-2-propenoxymethyl)-3-methylbutylamine:



[in which X is a leaving group].

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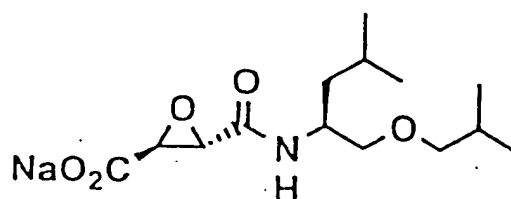
Description

[FIELD OF THE INVENTION]

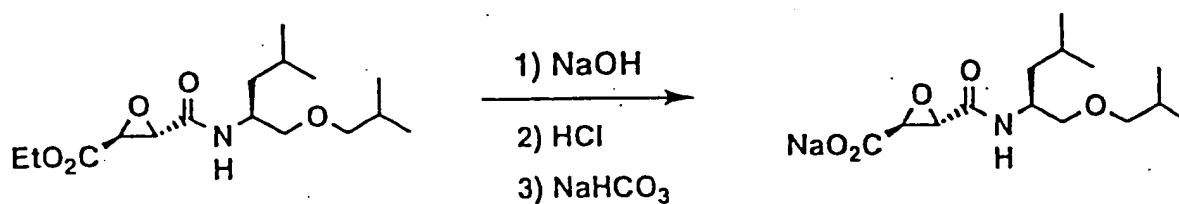
[0001] The present invention relates to an amine derivative and a process of production thereof.

[BACKGROUND OF THE INVENTION]

[0002] The under-illustrated sodium (2S,3S)-3-[[[(1S)-1-isobutoxymethyl-3-methylbutyl]carbamoyl]oxirane-2-carboxylate (hereinafter referred to as Compound A) shows a cathepsin-inhibitory action and is useful as a remedy for treating rheumatoid arthritis and osteoporosis (Patent reference 1: WO 99/11640 pamphlet):



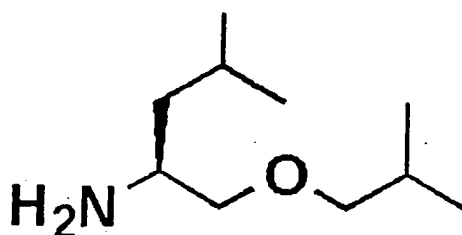
[0003] Patent reference 1 describes a process for producing Compound A according to the following reaction scheme (see Example 48 of Patent reference 1):



[0004] There is a need to provide an industrially employable synthesis process for the production of Compound A.

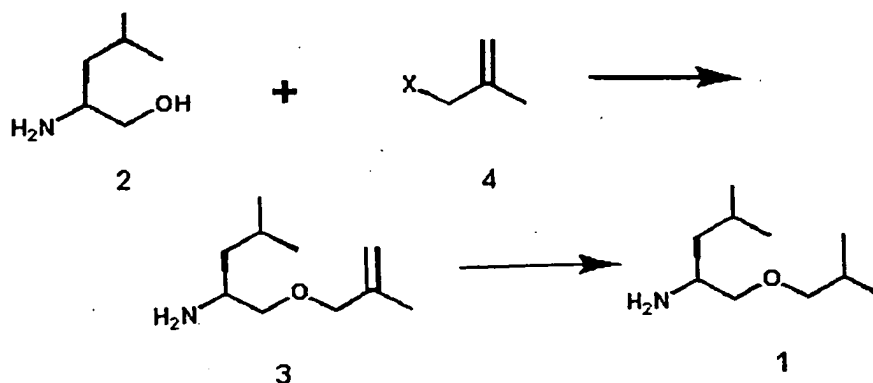
[DISCLOSURE OF THE INVENTION]

[0005] The present invention has an object to provide an amine derivative employable as an intermediate compound for the synthesis of Compound A. The amine derivative is (1S)-1-isobutoxymethyl-3-methylbutylamine represented by the following formula:



[0006] The invention also has an object to provide a process for producing the amine derivative.

[0007] The (1S)-1-isobutoxymethyl-3-methylbutylamine can be obtained according to the following reaction scheme:



Step 1: L-leucinol (2) → Compound (3)

[0008] The reaction of L-leucinol (2) with the compound (4) can be performed in such a solvent not participating in the reaction as THF or DMSO at a temperature between -30°C and the reflux temperature in the presence of a base.

[0009] Examples of the leaving groups represented by X in the compound (4) include halogens such as chlorine, bromine and iodine, p-toluenesulfonyloxy, and methanesulfonyloxy.

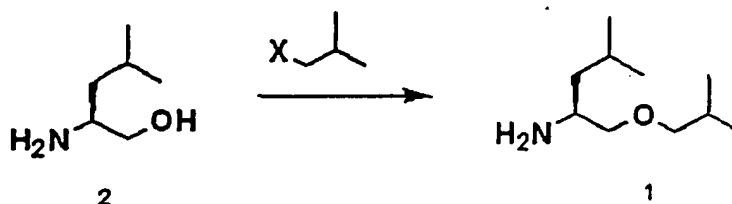
[0010] Examples of the bases include alkali metal hydrides such as NaH, LiH and KH, alkaline earth metal hydrides such as CaH₂, alkali metal alkoxides such as t-BuOK, inorganic bases such as NaOH and KOH, and organic bases such as triethylamine

[0011] The starting compound, namely L-leucinol, can be obtained by reducing L-leucine (for example, United States Patent 3,935,280).

Step 2: Compound (3) → Compound (1)

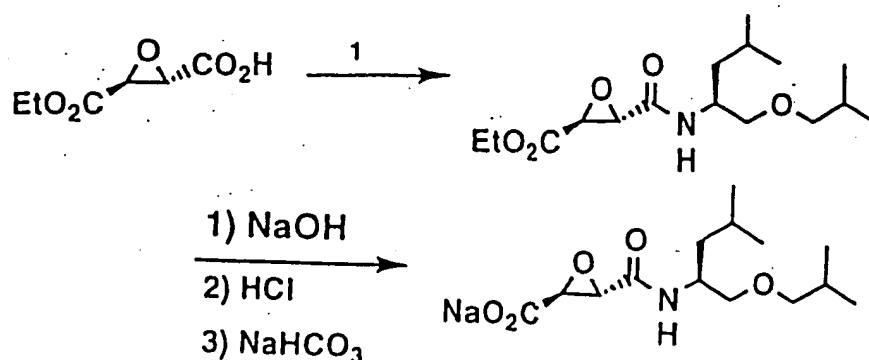
[0012] The reaction can be performed in such a solvent not participating in the reaction as ethanol or acetic acid at a hydrogen pressure of 1 to 100 atm., using 0.1 to 20 % of such a catalyst employable for catalytic reduction of a double bond as Pd/C or Raney nickel.

[0013] The (1S)-1-isobutoxymethyl-3-methylbutylamine also can be produced according to the following reaction scheme:



[in which X has the same leaving group as above].

[0014] The aforementioned Compound A can be produced from the (1S)-1-isobutoxymethyl-3-methylbutylamine obtained above according to the following reaction scheme (see Examples 48 and 18a of Patent reference 1):



[0015] The process of the invention can give the amine derivative, i.e., (1S)-1-isobutoxymethyl-3-methylbutylamine, in a high yield. The aforementioned Compound A can be obtained from this amine derivative in a high yield.

[0016] The invention is further described by the following examples.

[Example 1] (1S)-1-(2-methyl-2-propenoxyethyl)-3-methylbutylamine

[0017] To a solution of L-leucinol (20.0 g, 0.17 mol) in an anhydrous THF (200 mL) was portionwise added 60% NaH (7.92 g, 0.198 mol). The resulting mixture was stirred for 30 min. at room temperature and further for 2 hours at 50°C. The mixture was then cooled to room temperature. To the resulting suspension was dropwise added a solution of 3-chloro-2-methylpropene (15.45 g, 0.17 mol) in an anhydrous THF (50 mL). The resulting mixture was stirred for 20 hours at room temperature. The THF was distilled off under reduced pressure. To the residue were successively added a mixture of ice and water and diethyl ether. The mixture was stirred for 5 min. at room temperature, and the organic portion was separated. The aqueous portion was subjected to extraction with diethyl ether. The extract was combined with the organic portion. The combined organic portion was washed with 1 mol/L aqueous hydrochloric acid (7 mL) and subjected to extraction with 1 mol/L aqueous hydrochloric acid (153 mL). The resulting hydrochloric acid extract was made to approx. pH 10 by addition of potassium carbonate and subjected to extraction with diethyl ether. The organic portion was washed with water, dried over sodium sulfate, and placed under reduced pressure to distill the solvent off. There was obtained the titled compound (20.22 g, 69.2%) as an oily product.

¹H-NMR (CDCl₃) δ: 0.90 (3H, d, J=7Hz), 0.93 (3H, d, J=7Hz), 1.1-1.3 (2H, m), 1.74 (3H, s), 1.7-1.8 (1H, m), 2.62 (2H, broad s), 3.0-3.1 (1H, m), 3.15 (1H, dd, J=8Hz & 9Hz), 3.38 (1H, dd, J=3Hz & 9Hz), 3.88 (1H, d, J=13Hz), 3.92 (1H, d, J=13Hz), 4.89 (1H, s), 4.96 (1H, s).

[Example 2] (1S)-1-Isobutoxymethyl-3-methylbutylamine

[0018] A suspension of (1S)-1-(2-methyl-2-propenoxyethyl)-3-methylbutylamine (51.9 g, 0.3 mol) and 5%Pd/C (10.4 g) in ethanol (520 mL) was stirred for 18 hours at room temperature in a hydrogen atmosphere (1 atm.). To the resulting reaction mixture was added 6 mol/L aqueous hydrochloric acid (52 mL) under cooling in ice bath. The aqueous mixture was subjected to filtration using celite for removing insolubles and then placed under reduced pressure for distilling the solvent off. The residue was dissolved in water, and the resulting aqueous solution was made to approx. pH 10 by addition of potassium carbonate. The solution was subjected to extraction with diethyl ether. The organic portion was dried over sodium sulfate and placed under reduced pressure for distilling off the solvent. There was obtained the titled compound (48.6 g, 92.6%) as an oily compound.

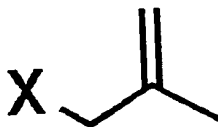
bp: 66-67°C/5 mmHg

¹H-NMR (CDCl₃) δ: 0.90 (3H, d, J=6Hz), 0.90 (3H, d, J=6Hz), 0.91 (3H, d, J=6Hz), 0.93 (3H, d, J=6Hz), 1.1-1.2 (2H, m), 1.50 (2H, broad s), 1.6-1.8 (1H, m), 1.8-1.9 (1H, m), 3.0-3.1 (1H, m), 3.11 (1H, dd, J=8Hz & 9Hz), 3.16 (1H, dd, J=7Hz & 9Hz), 3.23 (1H, dd, J=7Hz & 9Hz), 3.37 (1H, dd, J=3Hz & 9Hz).

Claims

1. (1S)-1-Isobutoxymethyl-3-methylbutylamine.
2. A process for preparing (1S)-1-isobutoxymethyl-3-methylbutylamine which comprises reducing (1S)-1-(2-methyl-2-propenoxyethyl)-3-methylbutylamine.

3. A process for preparing (1S)-1-isobutoxymethyl-3-methylbutylamine which comprises the steps of:
reacting L-leucinol and a compound having the following formula:



in which X is a leaving group,
in the presence of a base, to give a (1S)-1-(2-methyl-2-propenoxymethyl)-3-methylbutylamine, and
reducing the (1S)-1-(2-methyl-2-propenoxymethyl)-3-methylbutylamine.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP03/11468

A. CLASSIFICATION OF SUBJECT MATTER Int.Cl ⁷ C07C213/08, 217/08		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) Int.Cl ⁷ C07C213/08, 217/08		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) CA (STN), REGISTRY (STN)		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 99/11640 A1 (Nippon Chemiphar Co., Ltd.), 11 March, 1999 (11.03.99), Page 16; example 48 & EP 1022276 A1	1-3
☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.		
* Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family	
Date of the actual completion of the international search 26 September, 2003 (26.09.03)		Date of mailing of the international search report 21 October, 2003 (21.10.03)
Name and mailing address of the ISA/ Japanese Patent Office		Authorized officer
Facsimile No.		Telephone No.

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